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Behavioral and Physiological Effects of Leukotriene C_4

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ABSTRACT. **Leukotriene C_4 (LTC_4), a lipoxygenase metabolite of arachidonic acid, is a biological mediator of vasoregulation, pulmonary activity, shock, and inflammation, that has been demonstrated to have radioprotective efficacy. The effects of LTC_4 on locomotor activity, rectal temperature and hematocrit were examined. Subcutaneous administration of doses of 1.0 μg LTC_4/mouse or less did not affect locomotor activity. Doses of 5 or 10 μg LTC_4/mouse, however, resulted in almost complete cessation of locomotion within 12–14 min following treatment. At these doses, activity was suppressed for 2 h with complete recovery by 3 h postinjection. While a dose as high as 10 μg LTC_4 did not affect rectal temperature, 5 and 10 μg LTC_4 resulted in hematocrit increases of 10% and 40% respectively. Hematocrit returned to baseline within 1 h after a 5 μg pretreatment of LTC_4, and by 3 h following a 10 μg pretreatment. The duration of LTC_4-induced locomotor suppression did not correlate with previously determined durations of LTC_4-induced radioprotection.**

INTRODUCTION

The leukotrienes have emerged as an important class of biological mediators, although little information is available regarding their effects on behavioral processes. They have physiological roles in vasoregulation (1–7), neurotransmission (8, 9), hormonal regulation (9, 10), smooth muscle contraction (9, 11), and may also participate in inflammatory processes (9, 12), anaphylactic shock (9, 11) and asthma (9, 13). The peptide leukotrienes are derived from arachidonic acid through the lipoxygenase pathway and consist of leukotrienes (LT) C_4, D_4, and E_4. Some biological activities attributed to LTC_4 may be indirect through its conversion to LTD_4 or LTE_4. Each of these compounds is biologically active and generally elicits biological responses through interaction with specific receptors on the cell surface of the target tissue (14). Some biologioal activities are induced directly by LTC_4. Others may be mediated its conversion to LTD_4 or LTE_4. Activation of the receptor sometimes initiates synthesis of other eicosanoids or biological mediators (9, 11, 12). Unlike prostaglandins (15), leukotrienes are not capable of crossing the blood/brain barrier (16), although they may be synthesized by brain tissue (12, 17).

Responses to eicosanoids may vary from tissue to tissue and between species. LTC_4, for example, results in vasodilation and increased blood flow in the skin of humans (7), but is vasoconstrictive in the dog coronary artery (18, 19). Direct administration of LTC_4 into the brain has been shown to alter behavior in rats (20).

LTC_4 has recently been shown to protect V79AO3 Chinese hamster fibroblasts in culture (21), and mouse hematopoietic stem cells in vivo from damage by ionizing radiation (22). It also enhances the survival of mice exposed to an otherwise lethal dose of gamma radiation (23). Leukotriene treatment must be administered prior to irradiation to elicit protection (22, 23). In mice, optimal radioprotection of hematopoietic stem cells is induced by LTC_4 treatment 5–15 min before radiation exposure. A pretreatment of 10 μg LTC_4 per mouse provides a dose reduction factor (DRF) of 1.6 for exogenous spleen colony forming units (CFU-S), and a DRF of 2.0 for granulocyte macrophage progenitor stem cells (22).

Radioprotectors are advantageous for both civil defense and clinical use. In a civil defense setting, agents that maximize protection from radiation in-

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jury with minimal suppression of behavior are required. In the clinic, behavioral side effects are less critical, and compounds that selectively protect normal tissues can be used to enhance the therapeutic efficacy of radio- and chemotherapy.

Because of the important biological roles and the significant radioprotection afforded by LTC_4 (22), we have investigated the time course of some behavioral and physiological responses of this compound. In this paper we describe the effects of subcutaneous administration of LTC_4 on locomotor behavior. Further, because LTC_4 is known to affect body temperature (20) and hematocrit (5) in rats, these parameters were monitored to determine if alterations in behavior were associated with these measures.

MATERIALS AND METHODS

Subjects

Male CD2Fl male mice, 10–12 weeks old (20–25 grams) were obtained from Charles River Breeding Laboratory (Raleigh, NC). They were quarantined on arrival and representative animals were screened for evidence of disease. Mice were housed in groups of 8–10 in Micro-Isolator cages on hardwood chip contact bedding in an AAALAC accredited facility. Rooms were maintained at 21 +/− 1 C with 50% relative humidity on a reversed 12–12 hr light-dark cycle with lights off at 2 pm. Commercial rodent chow (Wayne Rodent Blox) and aciditied water (pH, 2.5) were freely available. All mice were euthanized by inhalation of carbon dioxide at the end of the experiment.

Drug

LTC_4 was the generous gift of Dr. J. Rokach (Merok-Frosst Laboratories, Pointe Claire-Dorval, Canada). It was dissolved in physiological saline, and administered to mice subcutaneously (s.c.) in the nape of the neck in a volume of 100 μl. Each animal received a single injection of either the saline vehicle or 0.1, 1, 5 or 10 μg LTC_4 (N = 9–10/group).

Locomotor activity measurement

A computerized Digiscan Animal Activity Monitory (Model RXYZCM-16, Omnitech Electronics, Columbus, Ohio) was used to quantitate locomotor behavior. This system has been previously used to monitor the effects of a number of radioprotective agents on locomotor activity, including prostaglandins (24, 25). Briefly, the apparatus used an array of infrared photodetectors spaced 2.5 cm apart to determine total distance travelled (horizontal activity; ambulation) and vertical sensors to record the number of vertical movements (vertical activity; rearing). The test chamber consisted of a 20 × 20 × 30.5 cm Plexiglas arena. The horizontal and vertical detectors were positioned 1.3 and 6.3 cm, respectively, above the floor of the arena.

Immediately following injection of LTC_4, animals were placed into the activity monitor where horizontal and vertical activity were recorded every 2 min for 1 h to ascertain the behavioral onset of the drug. Thereafter, activity was recorded at 1 h intervals for the next 2 h, after which time all groups had returned to control levels. All testing took place during the dark portion of the light-dark cycle. After each test, the apparatus was cleaned with a 50% alcohol solution.

Temperature measurement

Rectal temperatures were monitored using a Thermistar Thermometer (Model 8110–20, Cole-Parmer, Chicago, IL) thermister probe (Model #423, Yellow Springs Instruments, Yellow Springs, OH). The probe was inserted 2 cm into the rectum and secured in place to the tail by a 2.5 cm strip of adhesive tape. It remained in place during the 3 h measurement period during which time the mice were restrained. The study was conducted in an environmentally controlled room set at 22° C. Mice received either s.c. injection of the saline vehicle (N=7) or 10 μg LTC_4 (N=7). The rectal temperature was recorded every 5 min for the first hour and at 30 min intervals for the next 2 h.

Hematocrit

Animals received a s.c. injection of 0 (saline vehicle), 0.1, 1.0, 5.0, or 10.0 μg LTC_4 in saline (N=5–17/group). Mice were anesthetized with methoxyflurane (Pitman-Moore, Inc., Washington Crossing, N.J.) and blood samples for hematocrit determinations were obtained from the retro-orbital sinus. Measurements were made in duplicate and each animal was bled only once, at 0, 10, 60, or 120 min following LTC_4 treatment.

Statistical analysis

One-way analysis of variance was used to determine significance levels for the effects of LTC_4 on locomotor activity and rectal temperature. Post hoc comparisons were made using Dunnett's test. Mean values of the hematocrit were compared to the control group using Student's t-tests.

RESULTS

Locomotor activity

LTC_4 produced a dose-dependent decrease in

locomotor activity. Doses of 0.1 and 1.0 μg did not significantly alter locomotor behavior compared to control values. Doses of 5.0 and 10.0 μg, however, resulted in pronounced reductions in locomotion. At these dosages, both ambulation and rearing were significantly reduced from control values within 6 min of injection and maximal effect (a decrement of 95–100%) was observed at 12–14 min. During the second hour, postinjection locomotor activity was approximately 50% of controls. All animals fully recovered locomotor performance by the third hour following drug administration. Since the time course and magnitude of the response for both horizontal and vertical activity were very similar, only one parameter (vertical activity) is illustrated in Figures 1 and 2.

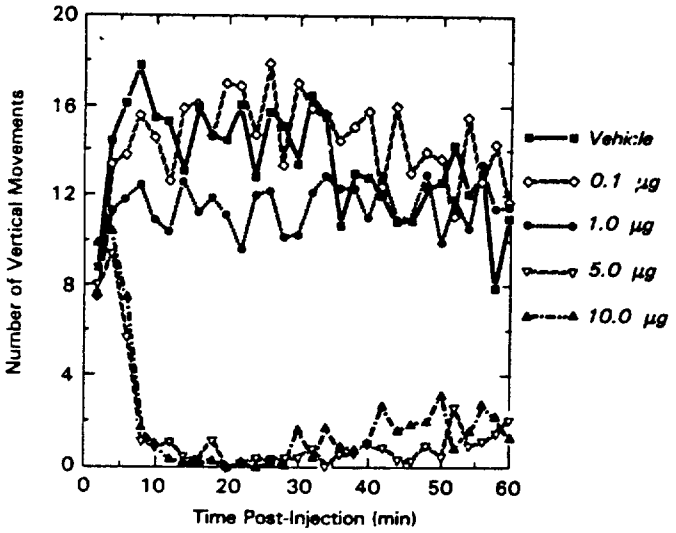

Fig. 1 Time course of leukotriene C_4 as a function of dose on vertical activity (rearing) during the first 60 min after injection (N= 9–10/group). Activity counts are presented in 2 min intervals. LTC_4 was administered subcutaneously immediately prior to assessment of locomotor activity. Maximal effect was reached 12–14 min postinjection. Similar results were obtained for horizontal activity (data not shown).

Rectal temperature

There were no significant differences in the rectal temperature of mice treated with saline or 10 μg LTC_4 (Fig. 3). The temperature of both the control and LTC_4 treated mice decreased as a function of time and is likely related to the duration of restraint.

Hematocrit

A dose-dependent increase in the hematocrit was observed in animals receiving LTC_4 (Table). Although no change in hematocrit was observed following doses of 0.1 or 1.0 μg/mouse, administration of 5.0 and 10.0 μg LTC_4 resulted in a 10% and 40% increase compared to controls, at 10 min postinjection. At 1 h after drug administration the 5.0 μg group had returned to control levels. Mice receiving 10.0 μg still had a 10% elevation in hematocrit at 2 h postinjection, and returned to normal by the third hour following treatment.

DISCUSSION

Doses of LTC_4 which have previously been shown to be radioprotective (5 to 10 μg LTC_4/mouse which is equivalent to 200 to 400 μg/kg body weight) (22, 23) resulted in a rapid reduction in locomotor activity and significant increases in the hematocrit, although rectal temperature remained unaffected. The decrease in locomotor behavior was dose dependent. While doses of 1 μg or less did not alter locomotor activity, administration of 5 and 10 μg LTC_4 resulted in almost total cessation of ambulation and rearing within 10–15 min after single s.c. injection. The animals did not fully recover from this reduction in activity until 3 h post-injection. Although this is the first study to report the effects of

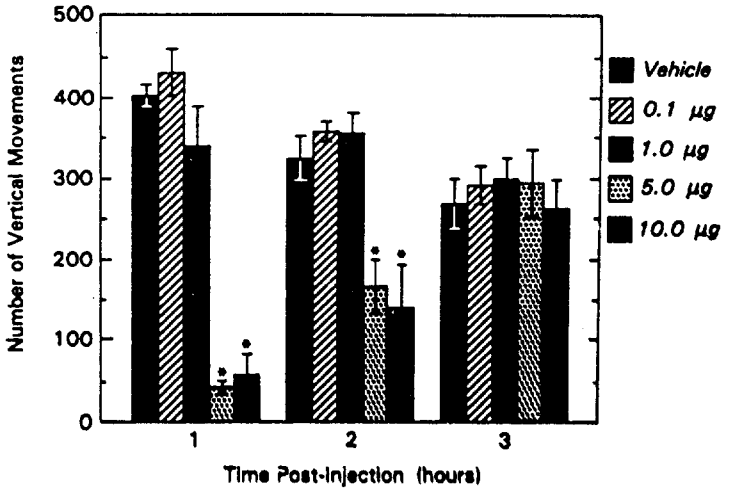

Fig. 2 Duration of action of the effects LTC_4 on vertical activity (rearing). By 3 h postinjection all groups had returned to control levels (N= 9–10/group). Horizontal activity showed a similar pattern of recovery (data not shown).
**Significantly ($p < 0.01$) from vehicle control group.

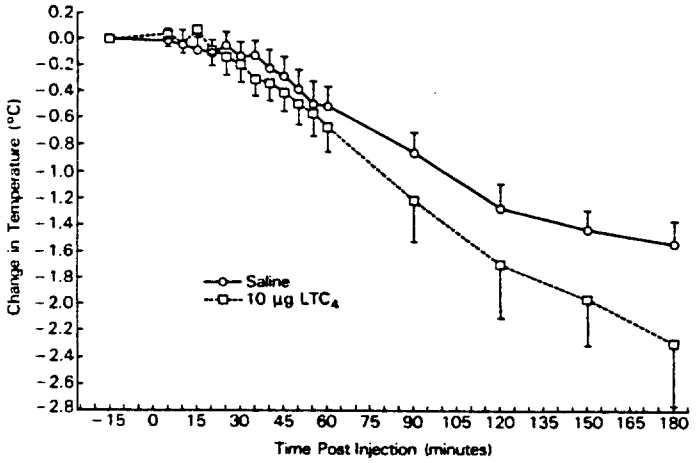

Fig. 3 Effect of LTC_4 (10 μg/mouse) on rectal temperature, expressed as the change in temperature from baseline levels taken 15 min prior to drug administration. There were no significant differences between the control mice and the LTC_4 group at any during the 3 h recording period (N=7/group).

Table Effect of LTC_4 on hematocrit

ug LTC4 per mouse	Time Post-Treatment 10 min	60 min	120 min	180 min
0.0	49.6 +/− 0.4	—	—	—
0.1	48.8 +/− 0.4	48.5 +/− 0.6	—	—
1.0	50.0 +/− 0.1	48.3 +/− 0.5	—	—
5.0	55.0 +/− 0.3***	48.6 +/− 1.1	—	—
10.0	69.6 +/− 1.4***	63.0 +/− 1.9***	54.8 +/− 1.3***	50.2 +/− 1.3

*** significantly different from control, $p < 0.0001$, t-test (N = 5–17/group)

s.c. administration of LTC_4 on locomotor behavior in mice, Brus et al (20) found that intracerebroventricular (ICV) administration of 1 μg of this compound to rats produced locomotor deficits that were apparent at 1 and 30 min after injection but not at 1 h. No decrease in locomotor activity was observed in mice in the present study following s.c. administration of 1 μg LTC_4.

Other eicosanoids such as prostaglandins of the E series result in a similar suppression of locomotor activity of rats (26), and we have recently described (24, 25) the decrease in locomotor behavior of mice treated with 16,16-dimethyl prostaglandin E_2 ($DiPGE_2$). Pretreatment with 40 μg/mouse $DiPGE_2$ provided a dose reduction factor (DRF) of 1.72 for animal survival following gamma irradiation (27). $DiPGE_2$ reduction of locomotor activity was dose dependent and required up to 30 h after administration of 40 μg/mouse to return to normal.

The decrease in ambulation and rearing by LTC_4 is comparable to that observed for 200 mg/kg of WR-2721, a thiol radioprotective agent with a DRF at this dose of approximately 1.6 (28–30). Although LTC_4 contains a thiol ether, the radioprotective action is not believed to act by a thiol free radical scavenging mechanism (22). In terms of radioprotective efficacy, five times more endogenous spleen colonies (E-CFU) survive irradiation when animals are pretreated with 10 μg LTC_4 than for mice receiving equivalent doses of LTD_4 or LTE_4 (22). This indicates that the radioprotection is attributable to the effects of LTC_4 rather than its conversion to LTD_4 or to LTE_4. The extent to which LTC_4 mediated behavioral effects may be due to other leukotrienes has yet to be determined.

Subcutaneous administration of doses of LTC_4 (10 μg) that induced radioprotection (22), reduced locomotor activity, and elevated the hematocrit, did not significantly affect rectal temperature. A similar lack of temperature response was observed in rats receiving 1 μg LTC_4 by ICV (31) or intrapreoptic administration (32). A decrease in body temperature, however, was observed in rats 10 min following an ICV injection of 7.5 μg LTC_4 (20). Possible effects of leukotrienes on temperature elevation have been implied from LTC_4 measurements in tissue biopsies of women with dysmenorrhea (33).

Although LTC_4 can be produced by nerve tissue (9, 17) and act as a neurotransmitter (8), it is not capable of crossing the blood/brain barrier (16). Therefore, it is unlikely that the rapid onset in suppression of locomotor behavior is the result of a

direct action on the central nervous system. The decreased activity observed in the present study may either result from intermediate messengers produced by the leukotriene, or in response to the physiologioal action of LTC_4. Some physiological responses to leukotrienes are mediated by inducing synthesis of other eicosanoids, such as thromboxanes and prostaglandins (11) that in turn produce the biological response. Prostaglandins are known to cross the blood/brain barrier (15) and to suppress locomotor activity (24–26).

Leukotrienes have direct potent activity on constriction of tracheal and bronchial smooth muscle (9, 11) and also vasoactivity (1, 4, 7, 17). Within 10 min after treatment with doses of LTC_4 that produced a behavioral decrement (5 and 10 μg/mouse), hematocrit levels had increased by at least 10% and 40% respectively. Increases in hematocrit and mean arterial blood pressure have been reported previously following intravenous administration of LTC_4 to rats (5, 6). Moreover, LTC_4 is known to promote plasma leakage from the vasculature (1). The short latency for the reduction in locomotor activity may reflect the rapid physiological responses induced by LTC_4. A 10% or greater elevation in hematocrit would likely increase resistance to blood flow, in turn reducing oxygen delivery. LTC_4 has been previously shown to decrease coronary flow (18, 19) with a concomitant reduction in contractile force (34). A reduction of blood flow to the heart could affect locomotor activity, although we have not determined if LTC_4 induces vasoconstriction of mouse coronary arteries. However, a decrease in the quantity of blood obtained from mice by cardiac puncture was observed at times corresponding to the increase in hematocrit and optimal period for radioprotection following administration of LTC_4 (T. L. Walden, Jr., unpublished).

Maintenance of the duration of the locomotor decrement does not appear to be associated with the physiological responses producing the hematocrit elevation. With 5 μg LTC_4, locomotor behavior was reduced by 88% within 1 h and 50% by 2 h post-treatment (Fig. 2). In a parallel study (Table), the hematocrit, after 5 μg LTC_4, had returned to normal within 1 h. In addition, the duration of the radioprotective action of LTC_4 (22) does not follow the same time course as that found for the suppression of locomotor behavior. Administration of 10 μg LTC_4 5–15 min prior to radiation exposure resulted in optimal radioprotection to mouse hematopoietic stem cells. At this dose, the protective activity was lost by 90 min post-treatment (22), while locomotor activity did not return to control level until 3 h after LTC_4 administration.

The toxic effects of radioprotectors are well established and occur at both the cellular and tissue levels (35). We have observed that the onset of behavioral toxicity as measured by locomotor activity decrements corresponds to the optimal pre-radiation treatment time for a variety of radioprotective compounds including LTC_4 (this study), $DiPGE_2$ (24, 25), WR-2721 (28–30) and glucan (36). The duration of the radioprotective effect for each of these is shorter than the behavioral decrement. We are continuing to explore the use of the locomotor activity test as an effective means to predict the optimal pre-radiation time for administration of radioprotectant compounds.

It may also be possible to mitigate the behavioral toxicity of LTC_4 without altering its radioprotective properties. This could be accomplished by co-administration of LTC_4 with agents that reverse the behavioral disruption. Alternatively, it may be feasible to develop LTC_4 analogs that retain the radioprotective or other clinically beneficial properties without the production of concomitant behavioral side-effects. In addition, it is likely that a mixture of radioprotective agents that act by different mechanisms will be required to provide a radioprotective compound that will offer effective protection from ionizing radiation with minimal toxicity.

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